Cefuroxime in Renal Insufficiency: Therapeutic Results in Various Infections and Pharmacokinetics Including the Effects of Dialysis

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The expanding use of dialysis and transplantation has greatly prolonged the survival of patients with renal failure. This increasing population is, however, particularly susceptible to infection, often due to multiresistant nosocomial strains.

Cefuroxime (O'Callaghan *et al.* 1976) is a new semisynthetic cephalosporin with excellent antibacterial activity against many resistant organisms, since it is not easily destroyed by β-lactamases produced by Gram negative bacteria. These enzymes are responsible for bacterial resistance to the older cephalosporins in the largest proportion of strains.

This property of cefuroxime has rendered it active against many strains of *Proteus* spp (indole positive) and *Enterobacter* spp, which are uniformly resistant to the conventional cephalosporins.

The pharmacokinetics of cefuroxime have been studied in volunteers (Foord 1976) and patients with normal renal function (Daikos *et al.* 1977) and normal doses have been found to produce high serum levels after parenteral administration, which persist for several hours without risk of accumulation. Other desirable properties of cefuroxime are low protein binding and metabolic stability.

We have conducted a clinical trial of cefuroxime, the first results of which have been reported elsewhere (Daikos *et al.* 1977). Cefuroxime was found effective in a variety of infections, including several cases due to indole positive *Proteus*, without side effects or toxicity. Some patients with renal failure were treated from the beginning of the trial, since their infection was due to organisms sensitive to cefuroxime only. The trial was later extended to include more cases of infection during renal failure and our results in such infections are reported here.

The kinetics of cefuroxime in patients with various degrees of renal failure and the effects of dialysis were also studied and the results are also reported.

Patients and Methods

Thirty-three patients with renal failure were treated with cefuroxime (Table 1). Fourteen were males and 19 females. Their ages ranged from 15–78 years. The degree of renal failure was determined by the values of blood urea, serum creatinine and creatinine clearance (Cc) and they were grouped according to the value of the latter. Two patients were undergoing hæmodialysis and 9 peritoneal dialysis. Seventeen patients were suffering from infections of the urinary tract, 8 from respiratory infections and 8 from miscellaneous infections. Diagnostic criteria have been described in our previous report (Daikos *et al.* 1977). The dosage of cefuroxime varied according to the degree of renal failure and the severity of infection, ranging from 0.5–4.5 g daily for 7–28 days (Table 1).

The kinetics of cefuroxime were studied in 29 patients with renal failure (8 males and 21 females) aged 25–80 years, some of whom were given cefuroxime for the treatment of infection, but the majority of whom were studied as volunteers. Five patients were undergoing hæmodialysis and 3 peritoneal dialysis (Table 2). In addition, 4 patients with normal renal function were studied for comparison.

One gram of cefuroxime was given i.m. and specimens of blood and urine were taken before and at appropriate intervals after the dose. To study the effect of hæmodialysis, the dose was administered 1 h before the beginning of the session and blood was drawn before the dose, just before starting dialysis, at suitable intervals during dialysis (both arterial and venous) and at

Table 1

Dosage and duration of cefuroxime therapy in 33 patients with renal failure treated for a variety of infections

	No. pts	*Daily dose (g)*	*Duration (days)*
Cc 50–80	10	2–3	9–14
Cc 25–50	8	1.5–4.5	10–14
Cc 10–25	2	2	7–10
Cc < 10	2	2	7–10
Hæmodialysis	2	0.75–1	15–28
Peritoneal dialysis	9	0.5–3.2	7–20

Cc = creatinine clearance (ml/min)

Table 2

Analysis of 29 patients with renal failure in whom the kinetics of cefuroxime were studied

	No. pts
Cc 50–80	5
Cc 25–50	6
Cc 10–25	4
Cc < 10	6
Hæmodialysis	5
Peritoneal dialysis	3
Total	29

Cc = creatinine clearance (ml/min)

Table 3

Clinical and microbiological data and results of treatment with cefuroxime in 33 patients with infection complicating renal failure

Pt No.	*Sex*	*Age*	*Cc (ml/min)*	*Diagnosis*	*Infective organism*	*Daily dose (g)*	*Duration (days)*	*Clinical result*	*Bacteriological result*
1	F	15	80	Acute pyelonephritis	*Enterobacter ærogenes*	3	9	FL	R
2	F	49	78	Bronchopneumonia	*Escherichia coli*	2	10	C	E
3	M	62	78	Carbuncle (neck)	*Staphylococcus aureus*	2	11	I	E
4	F	44	69	Lobar pneumonia	*Klebsiella pneumoniæ*	2	10	C	E
5	F	72	68	Recurrent pyelonephritis	*Proteus rettgeri*	3	10	C	E
6	M	75	67	Chronic osteomyelitis	*Staph. aureus*	3	14	I	P
7	M	68	58	Lobar pneumonia	*E. coli*	3	14	C	P
8	M	43	56	Bronchopneumonia	*Kl. pneumoniæ*	2	10	C	E
9	M	63	54	Acute pyelonephritis	*Proteus vulgaris*	3	9	C	E
10	F	66	51	Acute cholangitis	Not isolated	3	12	C	U
11	F	68	50	Lobar pneumonia	*E. coli+Pr. mirab.*	3	14	C	E
12	F	23	44	Acute pyelonephritis	*E. coli*	2	10	C	E
13	M	71	42	Recurrent pyelonephritis	*Pr. rettgeri*	2	10	C	P
14	M	30	40	Acute pyelonephritis	*Proteus mirabilis*	1.5	12	C	E
15	M	74	38	Acute pyelonephritis	*Kl. pneumoniæ*	2.25	10	C	E
16	F	78	35	Bronchopneumonia	Not isolated	3	14	C	U
17	M	55	29	Acute pyelonephritis	*E. coli*	2	10	C	E
18	M	58	26	Acute pyelosepticæmia	*E. coli*	4.5	11	C	E
19	F	73	25	Acute cystitis	*E. coli*	2	10	C	E
20	F	76	22	Acute pyelonephritis	*E. coli*	2	7	C	E
21	F	71	9	Acute pyelonephritis	*E. coli+Enterobacter cloacæ*	2	10	C	E
22	F	30	4	Acute puerperal infection	*E. coli*	2	7	C	E
23	M	62	PD	Acute pyelonephritis	*E. coli+Pr. morgani*	2+2.1[a]	8	C	E
24	F	65	PD	Acute peritonitis	*E. coli+Enterobacter ærogenes*	1.5+1.4	20	C	E
25	F	40	PD	Recurrent pyelonephritis	*E. coli*	1	10	C	E
26	F	31	PD	Septicæmia, pelvic abscess	*Pr. vulgaris+Ent. ærog.*	1+1.8	10	C	E
27	F	40	PD	Acute pyelonephritis	*E. coli*	1+1.8	8	C	E
28	M	68	PD	Bronchopneumonia	*Pr. rettgeri+Ent. ærog.*	1+1.8	7	I	P
29	F	65	PD	Peritonitis	*Staph. aureus*	0.5+3.6	12	I	R
30	M	72	PD	Peritonitis	*Kl. pneumoniæ*	0.5	8	C	P
31	F	58	PD	Chronic pyelonephritis	*Pr. vulgaris*	1	14	I	E
32	M	33	H	Bronchopneumonia	Not isolated	0.75	15	C	U
33	F	40	H	Recurrent pyelonephritis	*Pr. vulgaris*	1	28	C	E

Cc = creatinine clearance; F = female; M = male; C = cure; I = improvement; FL = failure; E = eradication; P = persistance; R = reinfection with symptoms; PD = peritoneal dialysis; H = hæmodialysis; U = unknown;
[a] = when 2 numbers appear in daily dose column the first corresponds to i.m. and the second to i.p. administration

the end of the session. The same patients were also studied when off dialysis on other occasions.

One gram was given i.v. at the end of a session and blood taken 1 and 48 h later. During peritoneal dialysis, fluids were collected both at the beginning and at the end of each outflow period.

Hæmodialysis was performed with Dasco-Sandoz single pass artificial kidneys with a blood flow rate always above 200 ml/min, and peritoneal dialysis with Travenol catheters and Baxter fluids with 1.5% dextrose.

Concentrations of cefuroxime were measured by an agar well plate method using large dishes (25 × 25 or 30 × 30 cm). Antibiotic standards and specimens (suitably diluted when necessary) were set up in triplicate. A very sensitive strain of *Bacillus subtilis* was used as assay organism.

RESULTS

Therapeutic Efficacy

The infecting organisms were *Escherichia coli* (10), *Klebsiella pneumoniæ* (4), *Enterobacter ærogenes* (1), *Proteus mirabilis* (1), *Proteus* spp indole positive (5), *Staphylococcus aureus* (3) and in 6 cases 2 organisms were responsible, at least 1 of which was an indole producing *Proteus* or *Enterobacter*. Twenty-five of the 36 isolated strains were resistant to cephalothin and 16 to gentamicin. In 2 cases of bronchopneumonia and one of cholangitis the pathogen was not isolated but the clinical, radiological, hæmatological, biochemical and all other relevant data were unequivocally diagnostic of a bacterial ætiology for the infection.

Twenty-seven patients were cured, 5 improved and 1 failed (Tables 3 and 4). All cases of acute

Table 4

Results of therapy for various infections with cefuroxime in 33 patients with renal failure

Diagnosis	*No. pts*	*Cure*	*Improvement*	*Failure*
Acute cystitis	1	1		
Acute pyelonephritis	11	10		1
Recurrent pyelonephritis	4	4		
Chronic pyelonephritis	1		1	
Lobar pneumonia	3	3		
Bronchopneumonia	5	4	1	
Cholangitis	1	1		
Osteomyelitis	1		1	
Carbuncle	1		1	
Post-partum infection	2	2		
Peritonitis	3	2	1	
Total	33	27	5	1

Table 5

Mean concentration and half-life of cefuroxime in serum of 25 non-anuric patients with various states of renal function after i.m. administration of 1 g

Creatinine clearance (ml/min)	*No. pts*	*Serum concentration (μg/ml ± s.d.) at indicated times (h)*								
		0.5	*1*	*2*	*4*	*6*	*8*	*12*	*24*	*Half-life (h)*
80	4	26.4 (±10.9)	28.5 (±14.9)	18.2 (±7.4)	10.6 (±5.2)	5.7 (±2.7)	2.8 (±1.4)			2.05 (±0.3)
50–80	5	28.4 (±14·4)	31.2 (±9.8	28.8 (±9.1)	15.0 (±7.9)	6.1 (±3.9)	3.1 (±2.2)	1.0 (±0.9)		2.03 (±0.67)
25–50	6	27.3 (±15.3)	32.4 (±25.3)	23.6 (±15.8)	12.8 (±5.4)	8.1 (±4.7)	5.6 (±4.2)	2.0 (±1.5)		2.55 (±0.5)
10–25	4	33.0 (±34.3)	43.1 (±38.3)	34.8 (±19.3)	31.8 (±22.2)		21.6 (±18.9)	14.3 (±14.5)	3.4 (±4.7)	5.05 (±1.2)
10	6	36.9 (±26.6)	55.8 (±30.4)	48.2 (±25.2)	47.6 (±20.8)		35.1 (±15.3)	25.2 (±8.8)	13.2 (±5.8	14.8 (±5.9)

cystitis, recurrent pyelonephritis, lobar pneumonia, cholangitis and post-partum infection were cured. Results in acute pyelonephritis, bronchopneumonia and peritonitis complicating dialysis were also satisfactory, with only one case not completely cured per group. Results that were short of excellent were observed in patients with mild renal failure and in those undergoing peritoneal dialysis, while all patients with moderate or severe renal failure and those undergoing hæmodialysis were cured. In 30 cases the organism(s) had been isolated and in 25 of these they were eradicated. Most of those that persisted were observed in non-urinary infections.

No side effects or toxicity were observed in any of the patients.

Pharmacokinetics

Concentrations of cefuroxime in sera of patients with normal renal function reached their peak 0.5–1 h after i.m. injection of 1 g. Mean levels at 1 h were 28.5 (±14.9) μg/ml and at 8 h 2.8 (±1.4) μg/ml, with a mean serum half-life of 123 (±18) min (Table 5).

In renal failure, levels were higher and more prolonged but only in severe forms were these differences appreciable (Table 5). In patients with a Cc of 50–80 ml/min, mean blood levels at 1 h were 31.2 (±9.8) μg/ml and at 8 h 3.1 (±2.2) μg/ml with a mean half life of 122 (±40) min. At a Cc of 25–50 ml/min, mean levels at 1 h were 32.4 (±25.3) μg/ml and at 8 h 5.6 (±4.2) μg/ml while the half life averaged 153 (±30) min. In patients with a Cc of 10–25 ml/min mean levels at 1 h were 43.1 (±38.3) μg/ml and at 24 h 3.4 (±4.7) μg/ml with a mean half life of 303 (±72) min. Patients with a Cc below 10 ml/min had 13.2 (±5.8) μg/ml of cefuroxime in blood at 24 h with a mean half life of 14.8 (±5.9) h.

In patients with anuria, off dialysis, mean blood levels 1 h after i.v. injection of 1 g of cefuroxime averaged 40 (±10.4) μg/ml and at 48 h 9.2 (±4.0) μg/ml with a half life of 21.9 (±4.1) h (Table 6). During hæmodialysis, the half life was shortened to 3.75 (±1.4) h and in peritoneal dialysis it was 13.6 (±4.4) h. The extraction ratio in hæmodialysis averaged 0.18.

Levels of cefuroxime in urine were very high even in advanced renal failure (Table 7). Patients with a Cc of more than 10 ml/min concentrated cefuroxime in their urine at levels exceeding 100 μg/ml for 12 h. In patients with a Cc below 10 ml/min, levels were often below 100 but still above 30 μg/ml in most collections. The mean recovery rate in normal renal function was 86.3% (±17.6) of the dose, but less in renal failure, falling to 5.4% (±3.5) in patients with a Cc below 10 ml/min.

Table 6

Mean concentrations and half-life of cefuroxime in serum of 8 anuric patients off and on hæmodialysis (5 patients) or peritoneal dialysis (3 patients) after injection of 1 g

	Serum concentration (g/ml ± s.d.) at indicated times (h)										
	0.5	*1*	*2*	*3*	*4*	*6*	*8*	*12*	*24*	*48*	*Half-life (h)*
Off dialysis		40 (±10.4)								9.2 (±4.0)	21.9 (±4.1)
Hæmodialysis A		23.9 (±1.4)	25.0 (±2.3)	23.4 (±1.9)	i9.2 (±2.3)						3.75 (±1.38)
Hæmodialysis V		18.5 (±1.7)	21.0 (±3.0)	19.2 (±2.6)	15.8 (±2.4)						
Peritoneal dialysis	44.2 (±9.1)	55.3 (±8.6)	61.9 (±13.1)		51.0 (±4.2)	37.8 (±4.5)	39.2 (±12.4)	26.9 (±6.0)	14.8 (±9.1)		13.6 (±4.4)

A = arterial blood; V = venous blood

Table 7

Mean urine concentrations and recovery rates of cefuroxime in 25 patients with various states of renal function after i.m. administration of 1 g

Creatinine clearance (ml/min)	*No. pts*	*Urine concentrations (μg/ml ± s.d.) at indicated collection periods (h)*						*Recovery rate %*
		0–2	*2–4*	*4–6*	*6–8*	*8–12*	*12–24*	
80	4	6860 (±5290)	2255 (±1438)	1368 (±1149)	775 (±715)			86.3 (±17.6)
50–80	5	4630 (±4995)	3550 (±2320)		1062a (±510)	98.3 (±92.8)		53.7 (±16.6)
25–50	6	1782 (±1566)	1853 (±1983)		723[a] (±579)	309 (±336)		44.1 (±18.1)
10–25	4	149 (±65)	162 (±50)		173[a] (±65)	284 (±396)	66.6 (±51.4)	12.6) (±5.4
10	6	28.2 (±29.2)	36.2 (±22.3)		66.3[a] (±68)	38.7 (±42.7)	24.7 (±15.6)	5.4 (±3.5)

[a] = values indicated correspond to collection periods of 4–8 h

Cefuroxime levels in peritoneal dialysate were around 15–20 μg/ml. At the beginning of each outflow period levels were lower, averaging 13.4 (±7.1) μg/ml in the first 12 h, but drug concentrations measured at the end of the outflow periods during the same 12 h averaged 23.2 (±9.4) μg/ml.

Discussion

A variety of infections complicating renal failure were treated with cefuroxime. The infecting organisms were often multiresistant and the drug had to be given empirically in the first cases, since its kinetics were not known. However, the results were excellent. In 33 patients there were 27 cures, 5 improvements and only 1 failure.

Treatment of urinary tract infections even in final stage renal failure was very successful, 15 out of 17 were cured, 1 improved and 1 failed. The latter was a 15 year old girl with acute leukæmia who developed acute pyelonephritis due to *Enterobacter ærogenes*. After initial improvement on cefuroxime (1 g i.v. three times daily) she relapsed clinically and *Pseudomonas æruginosa* was isolated from urine. We do not believe that her borderline renal insufficiency was a factor contributing to failure of cefuroxime therapy.

In view of the fact that the majority of the infecting organisms were resistant to cephalothin and 16 out of 36 resistant to gentamicin, our results must be considered very promising. The absence of side effects and toxicity are additional favourable points.

Results of kinetic studies in normal renal function are similar to our previous findings (Daikos *et al.* 1977). In these subjects, doses of 1 g i.m. every 6–8 h result in therapeutic blood levels for the greater part of the treatment period, without danger of accumulation. The same can be expected in mild or moderate renal failure, since the mean half-life was not more than 2.5 h.

When the Cc falls below 25 ml/min, however, an adjustment of dose is necessary; 1 g every 12 h seems safe and adequate. In patients with a Cc below 10 ml/min but who are not anuric, the average half-life was 14.8 h and levels after 24 h were 13.2 μg/ml. In these patients one should determine the half-life of cefuroxime. However, since this is often impossible to do quickly we recommend the following schedule: a loading dose of 1 g is to be followed by a maintenance dose every 24 h. The maintenance dose will be calculated by multiplying the patient's Cc (in ml/min) by 100 mg. For example, a patient with a Cc of 7 ml/min should receive maintenance doses of 700 mg every 24 h.

In anuria the mean serum half life was 21.9 h. Hæmodialysis was effective in removing cefuroxime, with an average half-life of 3.75 h and an extraction ratio of 0.18, while peritoneal dialysis was only moderately effective with an average half life of 13.6 h. We recommend that 1 g of cefuroxime be given at the beginning of hæmodialysis and 750 mg at the end. During peritoneal dialysis, 1 g should be given every 24 h.

Levels in urine were very high in our patients, even in advanced renal failure. This indicates that infections of the urinary tract can be treated with cefuroxime in these patients and our own excellent therapeutic results even in final stage renal failure support this point.

Infections of the peritoneal cavity can also be treated with cefuroxime, since levels in peritoneal dialysate were well above the minimum inhibitory concentrations of susceptible organisms.

Summary

Cefuroxime was given to 33 patients with various degrees of renal failure (2 on hæmodialysis and 9 on peritoneal dialysis), who were suffering from a variety of infections: 17 from urinary tract infections, 8 from infections of the respiratory tract and 8 miscellaneous infections. Responsible organisms included *Escherichia coli* (10), *Klebsiella pneumoniæ* (4), *Enterobacter ærogenes* (1), *Proteus mirabilis* (1), *Proteus* spp indole positive (5),

Staphylococcus aureus (3) and mixed pathogens (6). Twenty-seven patients were cured, 5 improved and 1 failed. Results of treatment of urinary tract infection were satisfactory even in final stage renal failure. No side effects or toxicity were noted.

The kinetics of cefuroxime were studied in 29 patients with renal failure (5 on hæmodialysis and 3 on peritoneal dialysis) some of whom were treated for an infection, but the majority of whom were volunteers. The mean serum terminal half life in patients with a Cc of 50–80 ml/min was 122 min, compared to a mean half life of 123 min observed in normal renal function. In more severe failure, mean half life was as follows: Cc 25–50: 153 min; Cc 10–25: 303 min; Cc <10: 14.8 h. Patients with anuria but off dialysis had an average half life of 21.9 h. On hæmodialysis this was 3.75 h and on peritoneal dialysis, 13.6 h. The extraction ratio in hæmodialysis averaged 0.18. Urinary levels of cefuroxime were very high, even in advanced renal failure and levels in peritoneal dialysate were adequate to treat peritonitis during dialysis.

Cefuroxime is a safe and effective drug for the treatment of infection in renal failure, including dialysis. A schedule for cefuroxime dosage in various degrees of renal failure is proposed.

REFERENCES

Daikos G K, Kosmidis J C, Stathakis C & Giamarellou H (1977) *Journal of Antimicrobial Chemotherapy* 3 (in press)

Foord R D (1976) *Antimicrobial Agents and Chemotherapy* **9**, 741

O'Callaghan C H, Sykes R B, Ryan D M, Foord R D Muggleton P W (1976) *Journal of Antibiotics* **29**, 29